REMARKS

Entry of the foregoing and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claim 33 has been amended to further clarify Applicants' invention. New claims 49-52 have been added. Support for new claims 49-52 can be found on page 12 (first paragraph) and in Example 8 (page 16) of the specification. No new matter has been added.

I. Rejections Under 35 U.S.C. § 112

The specification and claims 12, 14, 33, 35 and 48 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabling. Applicants respectfully traverse this rejection.

The ultimate question is whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the art to practice the claimed invention without undue experimentation. See, e.g., *Ex Parte Forman*, 230 U.S.P.Q. 546, 547 (PTO Bd. App. & Int. 1986). That some experimentation is necessary does not preclude enablement unless the amount of experimentation is unduly extensive. See, e.g., *U.S. v. Telectronics, Inc.*, 8 U.S.P.Q. 2d 1217, 1222 (Fed. Cir. 1988). Further, routine experimentation does not constitute undue experimentation. *Johns Hopkins University v. Cellpro, Inc.* 152 F.3d 1342, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998).

The specification combined with the knowledge of the skilled artisan provides sufficient guidance for one skilled in the art to practice the invention without undue experimentation.

It is known in the art what is meant by "antiprogestin." This term encompasses a very large number of fully conventional compounds (e.g., RU-486) and those mentioned on page 11 of the specification and in the references cited there, among many others. Further, dose ranges for antiprogestins are known in the art (see any of the references or others), and there are routine assays known in the art to determine if a particular compound possesses antiprogestin activity.

Pages 8 (last paragraph) and 11 (last paragraph) of the specification provide examples of antiprogestins and Example 8 provides an example of a dose range for an antiprogestin (i.e., 0.5-200 mg antiprogestin/day). Therefore, based on the foregoing, the skilled artisan can envision those compounds suitable to practice the invention as claimed, and the skilled artisan can ascertain if a compound is an antiprogestin without undue experimentation. The amount of experimentation, if any, is minimal or routine.

The Examiner alleges that the specification fails to provide sufficient working examples and that the working examples present in the specification are not exhaustive nor define the class of antiprogestin compounds required. There is no requirement that an applicant provide examples directed to each and every species of a claimed invention. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112 Para. 1, enable a broadly claimed invention without describing all species that the claim encompasses). The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The Examiner has stated that the pharmaceutical art is "unpredictable" requiring each embodiment to be individually assessed for physiological activity. As discussed above, there is no requirement that an applicant provide examples directed to each and every species of a claimed invention. Further, there is nothing "unpredictable" about assessing a compound to determine if it possesses antiprogestin activity (the compound either does or does not possess the desired activity). There are straightforward assays in the art for doing this.

Therefore, based on the foregoing, applicants submit that the specification provides sufficient guidance for one skilled in the art to practice the invention without undue experimentation, and respectfully request withdrawal of the objection to the specification and the rejection of claims 12, 14, 33, 35 and 48 under 35 U.S.C. § 112.

II. Rejections Under 35 U.S.C. § 103

Claims 12-14, 33-35 and 48 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Garfield et al. (U.S. Patent No. 5,470,847) and Teutsch et al. (U.S. Patent No. 4,447,424). Applicants respectfully traverse this rejection.

The claimed invention relates to a method of fertility control comprising administering to a subject in need thereof a synergistically effective amount of a nitric oxide synthase inhibitor in combination with an antiprogestin and a method of fertility control for a woman, comprising administering to a woman in whom pregnancy is not desired and at risk for becoming pregnant a synergistically effective amount of a nitric oxide synthase inhibitor in combination with an antiprogestin.

The Examiner must show that the cited references coupled with the general knowledge at the time of the invention contain some suggestion or incentive to motivate a skilled artisan to modify a reference or to combine references to achieve the claimed invention. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Further, the requisite motivation must flow from some teaching in the references that suggests the desirability or incentive to arrive at the claimed invention. *See In re Napier*, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir 1995) ("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.").

Garfield et al. relates to inhibiting ovulation by administering a nitric oxide synthase inhibitor alone or in combination with one or more of a progestin, an estrogen, and a luteinizing hormone-releasing hormone. Teutsch et al. relates to steroids and compositions thereof, one of which has anti-implantation activity. These two references teach different compounds that operate via different mechanisms. Thus, there is no motivation to combine these compounds to achieve the claimed methods.

Further, the cited references do not contain a suggestion or incentive to support the combination. Nowhere does either reference teach or suggest i) a method of fertility control comprising administering to a subject in need thereof a synergistically effective amount of a nitric oxide synthase inhibitor in combination with an antiprogestin or ii) a method of fertility control for a woman, comprising administering to a woman in whom pregnancy is not desired and at risk for becoming pregnant a synergistically effective amount of a nitric oxide synthase inhibitor in combination with an antiprogestin. Thus, the skilled artisan would not be motivated to modify or combine Garfield et al. and Teutsch et al. to achieve the claimed invention.

It appears the Examiner's argument is based on an "obvious to try" modification. However, applicants remind the Examiner that an "obvious to try" modification is an

insufficient basis to modify or combine references and that one cannot base a determination of obviousness on what the skilled artisan might try or find obvious to try. The cited references must suggest to one of skill in the art that a nitric oxide synthase inhibitor and a antiprogestin should be combined to control fertility and that the skilled artisan would have a reasonable likelihood of success. In this regard, the Federal Circuit has held that "both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure." *See In re Dow Chemical Co. v. American Cyanamid Co.,* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). The cited references, singly or in combination, do not suggest that one could successfully combine synergistically effective amounts of a nitric oxide synthase inhibitor and an antiprogestin to control fertility.

The Examiner must also show that the modification or combination of cited references must have a reasonable expectation of success. As stated above, this reasonable expectation of success must be provided by the cited references, not applicants' disclosure. *Id.* The cited references, singly or in combination, do not mention or suggest the claimed invention (*i.e.,* a method to control fertility by administering a synergistically effective amount of a nitric oxide synthase inhibitor and a antiprogestin).

Finally, the Examiner must show that the cited or combined references teach each and every limitation of the claimed invention (*See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997). As stated above, the Examiner acknowledges that the cited references do not teach i) the administration of a combination of a nitric oxide synthase inhibitor in combination with an antiprogestin nor ii) the administration of the combination post-coitally. The Examiner's allegation that most rodents ovulate post-coitally cannot be used to render obvious the post-coital administration to a human.

In addition, applicants have found that the administration of a nitric oxide synthase inhibitor and an antiprogestin has a synergistic effect whereby lower doses of both can be used. This synergistic effect of the combination can be seen in the attached figures (Applicants are preparing a Rule 1.132 Declaration to attest to these results).

In the first figure, applicants demonstrate that the administration of an iNOS-inhibitor or an antiprogestin alone has no effect on inhibiting implantation (see ● and ■). However, when the iNOS-inhibitor is combined with the antiprogestin, the % inhibition ranges from approximately 50% to 100% depending on the dose. In the second figure, the administration of the iNOS-inhibitor alone had no effect on inhibiting implantation (see ○). The

administration of the antiprogestin only had an effect on implantation at higher doses of antiprogestin (see ▲). However, when the iNOS-inhibitor is combined with the antiprogestin, the % inhibition is approximately 100% with a much lower dose of the antiprogestin (0.01-0.03mg versus 0.1-0.3 mg for antiprogestin alone). The third figure demonstrates that the combination of the NOS inhibitors L-NAME or aminoguanidine with the antiprogestin onapristone decreases the % of pregnancies and the number of implantation sites. Thus, the claimed combination works synergistically to control fertility.

The cited references do not render obvious this unexpected synergistic effect of the claimed combination.

Accordingly, based on the foregoing, applicants respectfully request withdrawal of the objection to the specification and the rejection of claims 12-14, 33-35 and 48 under 35 U.S.C. § 103.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney or agent concerning such questions so that prosecution of this application may be expedited.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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